REMARKS

Reconsideration of the above-identified application in view of the amendment above and the remarks below is respectfully requested.

No claims have been canceled or added in this paper. Claim 1 has been amended in this paper. Therefore, claims 1-11 and 34-55 are pending and are under active consideration.

Support for the present amendment to claim 1 may be found in the present specification, for example, in the passage spanning the paragraph bridging pages 14 and 15 through page 16, first full paragraph, and in the Examples.

Claims 49-55 stand rejected under 35 U.S.C. 112, first paragraph, "as failing to comply with the enablement requirement." In support of the rejection, the Patent Office states, amongst other things, the following:

> The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicant claims a method for the prophylaxis of psychoses using the compound of claim 1. The compound of claim 1 is a deuterated L-DOPA derivative. Dewar et al. (*Neuro-Psychopharmacology & Biological Psychiatry* 1985, 9(5-6), 675-680) disclose a deuterated L-DOPA derivative D_3-DL-dopa, which is shown to work in a similar manner as L-DOPA. While L-DOPA is well known for its use in treatment of Parkinson disease and other diseases where it's necessary to increase the level of dopamine, use of L-DOPA for treatment of psychosis is not recognized in the art. In fact, the art teaches away from use of L-DOPA for treatment of psychosis. For example, Weiner et al. (*Neurology*, 2000, 54(7), p1538) show that treatment of Parkinson's disease with L-DOPA induces Psychosis. There are no examples in the specification where applicant demonstrates treatment of psychoses using the compound of claim 1 or exemplifies involvement of compounds of claim 1 in a biological pathway which prior art has recognized as being involved with the onset of psychoses. Since Dewar et al have demonstrated that D_3-DL-dopa functions in a manner similar to L-DOPA, and D_3-

> DL-dopa is a compound of the instant invention, one of ordinary skill would expect the deuterated derivatives of L-DOPA instantly claimed to aid in the onset of psychoses, and not have a therapeutic effect as is instantly claimed.

Applicant respectfully traverses the subject rejection. As best understood by Applicant, the subject rejection appears to be predicated on the Patent Office's position that the claimed compounds are not effective in the prophylaxis of psychoses. Applicant respectfully notes that the Patent Office bears the burden of proof on this issue and must prove that a person of ordinary skill in the art, after having read the present specification, would have a reasonable basis for doubting the operability of the invention in the prophylaxis of psychoses. Applicant respectfully submits that the Patent Office has failed to meet its burden.

The only evidence provided by the Patent Office in support of its position is Weiner et al. Weiner et al. discloses that treatment of Parkinson's disease with undeuterated L-dopa includes Psychosis as an adverse drug reaction. However, Applicant is claiming the use of the claimed deuterated derivatives only in prophylactic use or for the use in Schizophrenia, when negative symptoms predominate (at the current therapy during the interval periods between acute psychotic phases (positive symptoms, hallucinations)). For these reasons, Weiner et al. is inapposite.

Accordingly, for at least the above reasons, the subject rejection should be withdrawn.

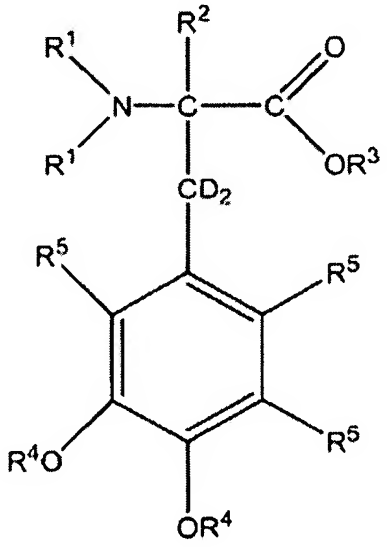
Claims 1, 11, 34-36 and 41 stand rejected under 35 U.S.C. 102(b) "as being anticipated by Dewar et al. (Neuro-Psychopharmacology & Biological Psychiatry 1985, 9(5-6), 675-680)." In support of the rejection, the Patent Office states the following:

> Dewar et al. disclose tri deuterated L-DOPA (D_3-DL-dopa), wherein the deuterium atoms are in α,α,β–positions of L-DOPA (page 675, lines 12-13 of the Introduction). The disclosed compound meets the structural limitations of claims 1 and 11.

Dewar et al also disclose pharmaceutical compositions (page 676 Section titled "methods", paragraph 2). They disclose treating L-DOPA with HCl and NaOH which would invariably form salts with L-DOPA.

Dewar et al disclose administering D_3-DL-dopa to animals with pretreatment with decarboxylase inhibitor (Paragraph 3 of methods) and measuring dopamine concentrations (paragraph 4 of methods).

Applicant respectfully traverses the subject rejection. Claim 1, from which claims 11, 34-36 and 41 depend, has been amended herein and now recites "Substantially isolated deuterated catecholamine derivatives of the general formula I



Formula I

wherein

R^1 is H or D, R^2 indicates H or D, R^3 is H, D, C_1-C_6 alkyl or C_5 to C_6-cycloalkyl, deuterated C_1 to C_6-alkyl or deuterated C_5 to C_6-cycloalkyl, R^4 indicates H or D and R^5 is H or D, and wherein at least one of R^1, R^2, R^3 and R^4 is D."

Thus amended, claim 1 is neither anticipated by nor rendered obvious over Dewar et al. for at least the reason that Dewar et al. fails to teach or to suggest the compound of Formula I, i.e., **the L-enantiomer, in a substantially isolated state**. Instead, Dewar et al. is limited to teaching DL-dopa and D_3-DL-dopa **racemates**. Dewar et al. provides absolutely no basis for a person of ordinary skill in the art to use the deuterated L-enantiomer in a substantially isolated state. Applicant respectfully submits that the use of the deuterated L-enantiomer of claim 1 leads to significantly improved pharmacokinetic and/or pharmacodynamic properties. The surprisingly improved properties of the deuterated L-enantiomer are illustrated, for example, in the response of June 15, 2007. Further evidence of such improved properties is provided below. This evidence is in the form of an experiment showing the dopamine output after application of different L-dopa derivatives.

Striatal dopamine output measured by microdialysis

The striatal output of dopamine was measured in Male Wistar rats following intraperitoneal administration of 50 mg/kg of L-2-Amino-2-deutero-3-(3,4-dihydroxyphenyl) propionic acid (alpha-deutero-L-DOPA), L-2-Amino-3,3-dideutero-3-(3,4-dihydroxyphenyl) propionic acid (beta-beta-dideutero-L-DOPA) and L-2-Amino-2,3,3-trideutero-3-(3,4-dihydroxyphenyl) propionic acid, compared to 50 mg/kg of L-2-Amino-3-(3,4-dihydroxyphenyl) propionic acid (L-DOPA). Male

wistar rats (BK Universal, Sollentuna, Sweden) weighing about 300 g at the time of experiment were anaesthetized with a cocktail containing fentanyl citrate (0.39 mg/kg) and fluanisone (12.5 mg/kg, Hypnorm®, Janssen-Cilag) and midazolam (6.25 mg/kg, Dormicum®, Roche) diluted in distilled water (1:1:2; 5 ml/kg i.p.) and mounted in a stereotaxic frame. Dialysis probes were implanted in the dorsolateral striatum (AP: +0.6: ML + 3.0: DV -6.2 relative to bregma and the dural surface according to the atlas of Paxinos and Watson (1998)). Dialysis occurs through a semipermeable membrane (Filtral AN69, Hospal Industrie, France) with an active surface length of 3.5 mm. Dialysis experiments were conducted approximately 48 h after surgery in freely moving rats. The rats received 30 min before administration of test items 10 mg/kg Carbidopa, (i.p.). The dialysis probe was perfused with a physiological perfusion solution (Apoteksbolaget, Sweden) at a rate of 2.5ml/min set by a microinfusion pump (Harvard Apparatus, Holliston, MA). Dialysate was collected over 15 min intervals and automatically injected into a high performance liquid chromatography (HPLC) system. On-line quantification of dopamine in the dialysate was accomplished by electrochemical detection (ESA, Chelmsford, MA). The location of microdialysis probes was verified in slices of formalin-fixed tissue stained with neutral red. The baseline corrected concentrations (fmol/min) were plotted over the time.

Comparison of AUC_{0-t} (area under the curve) values revealed that the increase of dopamine in the striatum following administration of 50 mg/kg of L-2-Amino-2-deutero-3-(3,4-dihydroxyphenyl) propionic acid (alpha-deutero-L-DOPA) and of L-2-Amino-3,3-dideutero-3-(3,4-dihydroxyphenyl) propionic acid (beta-beta-dideutero-L-DOPA) was about 25% less than after the same dose L-2-Amino-3-(3,4-dihydroxyphenyl) propionic acid (L-DOPA) (Table 1). This is in contrast to the

finding that the striatal dopamine output was significantly higher after 50 mg/kg of L-2-Amino-2,3,3-trideutero-3-(3,4-dihydroxyphenyl) propionic acid (alpha,beta,beta-trideutero-L-DOPA) as compared to L-DOPA (Table 1). Therefore, it was not predictable from the number and position of deuterium, whether a selectively deuterated L-DOPA derivative caused decreased or increased striatal dopamine levels.

Table 1: Median AUC of the baseline corrected dopamine output in the striatum

Compound	**AUC [% $AUC_{L\text{-}DOPA}$]**
L-2-Amino-3-(3,4-dihydroxyphenyl) propionic acid (L-DOPA)	100.00
L-2-Amino-2-deutero-3-(3,4-dihydroxyphenyl) propionic acid	75.92
L-2-Amino-2,3,3-trideutero-3-(3,4-dihydroxyphenyl) propionic acid	234.00
L-2-Amino-3,3-dideutero-3-(3,4-dihydroxyphenyl) propionic acid	75.77

The above experiment demonstrates that the claimed deuterated catecholamine L-enantiomers have unexpected significantly better pharmacodynamic effects than undeuterated catecholamines.

Accordingly, for at least the above reasons, the subject rejection should be withdrawn.

Claims 34-48 stand rejected under 35 U.S.C. 103(a) "as being unpatentable over Dewar et al. (*Neuro-Psychopharmacology & Biological Psychiatry* 1985, 9(5-6), 675-680)." In support of the rejection, the Patent Office states the following:

Scope of prior art

Dewar et al teach D_3-DL-dopa and its ability to replenish dopamine levels as is commonly practiced with L-DOPA (page 675, introduction, lines 1-2). Dewar et al also recognize the need to inhibit enzymes including decarboxylase (page 676, methods paragraph 3), monoamine oxidase (page 677, discussion, paragraph 1) and β-hydroxylase (page 677, discussion paragraph 2). Dewar et al only utilize decarboxylase inhibitor in their experiments.

Ascertaining the difference between prior art and instant claims

Instant claims are directed to methods for treatment of dopamine deficiency disease. While Dewar et al demonstrate the ability of D_3-DL-dopa to increase levels of dopamine in rats (see page 677, figure 1), they do not disclose an actual method of treatment using D_3-DL-dopa.

Obviousness

One of ordinary skill in the art at the time the invention was made would have [been] motivated by the disclosure of Dewar et al to utilize D_3-DL-dopa in treatment of dopamine deficiency diseases. Dewar et al. have demonstrated a faster rate of increase in dopamine concentration when compared to the L-DOPA (see figure 1). They have also recognized the need for enzyme inhibitors to inhibit the activity of β-hydroxylase, decarboxylase and monoamine oxidase. In order to avoid digestion of the D_3-DL-dopa by the enzymes one of ordinary skill would have been motivated to utilize inhibitors in treatment where D_3-DL-dopa is utilized and in pharmaceutical compositions comprising D_3-DL-dopa. Such inhibitors are known in the art (statement by the applicant in the specification, page 1, paragraph 3 through page 2 paragraph 2, is treated as admission of prior art). Combining D_3-DL-dopa with enzyme inhibitors to prepare pharmaceutical compositions and subsequent use of the said composition to treat dopamine deficiency diseases is therefore obvious.

Applicant respectfully traverses the subject rejection. Claims 34-48 depend from claim 1. Claim 1 is patentable over Dewar et al. for at least the reasons given above. Therefore, based at least on their respective dependencies from claim 1, claims 34-48 are patentable over Dewar et al.

Accordingly, for at least the above reasons, the subject rejection should be withdrawn.

Claims 2-10 stand objected to "as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims."

Applicant respectfully traverses the subject objection. The subject objection is predicated on the Patent Office's position that claim 1, the base claim from which claims 2-10 depend, is not allowable. However, as Applicant has explained above, claim 1 is now allowable. Therefore, for at least this reason, the subject objection should be withdrawn.

In conclusion, it is respectfully submitted that the present application is now in condition for allowance. Prompt and favorable action is earnestly solicited.

If there are any fees due in connection with the filing of this paper that are not accounted for, the Examiner is authorized to charge the fees to our Deposit Account No. 11-1755. If a fee is

required for an extension of time under 37 C.F.R. 1.136 that is not accounted for already, such an extension of time is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

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Dated: September 8, 2008

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on September 8, 2008

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